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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/563,110	06/19/2006	Hanne Muller	Q-92287	1130

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EXAMINER	
BETTON, TIMOTHY E	

ART UNIT	PAPER NUMBER
1617	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/563,110	MULLER ET AL.	
	Examiner	Art Unit	
	TIMOTHY E. BETTON	1617	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2008*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *18,21,24,27,33 and 36-38* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *18,21,24,27,33 and 36-38* is/are rejected.

7)☒ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants Remarks filed on 31 March 2008 have been received and duly made of record.

The essence of applicants arguments are drawn specifically to the Examiner's alleged failure to establish any motivation for combining the various references. Principally, applicants contend that:

(1) There is no disclosure in Kitagawa et al of microbial lipids according to the claims, nor of a method for reducing cholesterol.

(2) Barrows merely discloses a method for producing particles of a desired size.

(3) Rawlings et al is not concerned with using microbial lipids, nor is it a disclosure of a method for reducing plasma cholesterol in animals.
(4) Makula and Fang et al recite the phospholipid profiles of methanotrophic bacteria. Neither document suggests any uses for the phospholipids which they report.

Upon further consideration of the references incorporated in the last action, the rejection as filed is withdrawn.

Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set presently being applied to the instant invention.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

Claim 18, 21, 24, 27, 30, 33 and 36-38 are rejected under 35 U.S.C. 103(a) as being unpatentable over Eriksen et al. (USPGPUB 2004/0241790 A1) and Koffas (USPGPUB 2002/0110885 A1) in view of Makula et al. (as already made of record), Koffas et al. (USPGPUB 2002/0137190 A1) and Belloni et al. (USPN 6034137 A).

Eriksen et al. essentially teach a number of different protein-containing materials have been proposed as substitutes for more traditional sources of protein, such as fish meal, soya products and blood plasma, in **human foods** and as animal feeds. These materials include single-cell microorganisms such as fungi, yeasts and bacteria which contain high proportions of proteins [0002].

Eriksen et al. teach [that] besides being simply used as sources of biomass, microorganisms may be grown and harvested to serve as sources of useful chemicals, e.g. drug compounds, proteins, carotenoids, etc. [...] [t]he contents of which are hereby incorporated by reference) describe the use of **methanotrophic bacteria**, and in particular Methylomonas 16a (ATCC PTA 2402), for the preparation of carotenoids [0004].

Thus, based on the cited use, the intended function of administration could be interpreted as principally human consumption in view of useful chemicals being described as drug compounds, proteins, and carotenoids, etc. Eriksen, thus, describes sources of biomass which yield variable components which may extracted together or extracted apart from each other.

Eriksen et al. teach 60%-80% crude weight protein based on fermentation of the biomass [0058].

Eriksen et al. does not teach wherein said lipid is a phosphatidylethanolamine. Eriksen et al. **does not teach** lipids emphatically.

But it is worth noting, however, that in the instant specification applicants admit that the homogenization step [...] may be omitted and the biomass from the receptor may be subjected to a conventional lipid extraction technique (supercritical extraction or solvent extraction) (page 6). Thus, it may be interpreted that the biomass contains a varying degree of materials that may be extracted out separately depending upon the specific material required as cited by Eriksen, i.e., microorganisms may be grown and harvested to serve as sources of useful chemicals, e.g. drug compounds, proteins, carotenoids, etc.

In view of this, Koffas et al. (USPGPUB 2002/0110885 A1) establishes the nexus between carotenoids and bacterial lipids.

Koffas et al. teach methanotrophic cells can further build the oxidation products of methane (i.e. formaldehyde) into more complex molecules such as protein, carbohydrate and lipids. [...]. Similarly, methanotrophs are known to accumulate both isoprenoid compounds and carotenoid pigments of various carbon lengths [...]. Although these compounds have been identified in methanotrophs, they have not been microbial platforms of choice for production

because these organisms have very poorly developed genetic systems, thereby limiting metabolic engineering ability for chemicals [0006].

Accordingly, Makula teaches phospholipids of Methylococcus capsulatus, Methylosinus trichosporium, La Paz, and OBT were examined in relation to their qualitative and quantitative composition. M. Capsulatus exhibited a phospholipid composition consisting of **phosphatidylethanolamine**, phosphatidylglycerol, cardiolipin, and phosphatidyl-choline. The esterified fatty acids were predominantly C16:0 and C16: 1. M.trichosporium, La Paz, and OBT exhibited an essentially identical phospholipid composition consisting of phosphatidylmonomethylethanolamine, phosphatidyl-dimethylethanolamine, phosphatidylcholine, and phosphatidylglycerol. Only trace amounts (less than 1%) of cardiolipin were found in these organisms. The major esterified fatty acid in these organisms was C18: 1 (87 to 90%). The monounsaturated fatty acids from all four organisms consisted of both cis and trans isomers, each of which contained delta8, delta9, delta10, and delta11 double-bond positional isomers (Abstract only).

As disclosed above, Makula teaches phospholipids of Methylococcus capsulatus, Methylosinus trichosporium.

Makula et al. teach phosphatidylethanolamine, phosphatidylglycerol, cardiolipin, and phosphatidyl-choline.

Additionally, Makula et al. teach esterified fatty acids as being predominantly C16:0 and C16: 1.

Makula does not teach administration to fish or juvenile fish. Makula also does not teach a utility for phosphatidylethanolamine.

However, Koffas et al. (2002/0137190 A1) teach [...] different livestock animal types may have different nutritional requirements in terms of the relative proportions of protein to carbohydrate. Many carnivorous aquatic **fish** species, for example, have very high protein requirements. Ruminant livestock, on the other hand, thrive on higher fiber/carbohydrate diets. Methylomonas 16a has the capacity to form large amounts of carbohydrate, under certain conditions, in addition to the cellular protein which is always produced. Genes involved in gluconeogenesis (glycogen formation) or glycogen degradation might be altered or regulated such that glycogen content could either be decreased or increased. Thus the composition of the crude cell mass could be modulated to target high protein markets (lower carbohydrate) or alternatively, higher carbohydrate lower protein feed markets. The ability to engineer the composition of the microbe precludes the need to artificially formulate protein/carbohydrate ratios by exogenous additions [0156].

Further Koffas et al. (0137190 A1) teach methods of administration [that] the present invention provides a unique methanotrophic bacterial strain, useful for the production of a variety of materials from C1 carbon sources such as methane and methanol. The strain is referred to herein as Methylomonas 16a, and is characterized by rapid doubling time, high yield and the presence of genes encoding both the Entner-Doudcroff carbon pathway as well as the Embden-Meyerhof pathway, allowing for versatility in carbon flux management and higher efficiency of carbon incorporation. The strain has been shown to produce a variety of food and feed products such as single cell protein, exopolysaccharide and starch. The strain has particularly high value

in the production of food and feed materials as it is possible to manipulate the various concentrations of protein, carbohydrate and starch all within the same organism. **This capability will permit strains to be uniquely tailored for individual specific food and feed applications.** Additionally the strain has demonstrated utility in the production of terpenoid and carotenoid compounds, useful as pigments and as monomers in polymeric materials [0075].

Koffas et al. (0137190 A1) does not teach juvenile fish, however it is obvious based in the context of the teachings that any fish would have at one time have been a juvenile fish being administered these same food and feed formulations.

Further, Belloni et al. teach novel cationic lipids, particularly guanidino lipids, and methods for their preparation. Also provided are polyanionic-lipid complexes comprising the lipids of the invention, **their preparation and use to deliver** biologically active substances, particularly nucleic acids to cells (abstract only).

Belloni et al. teach examples of optional co-lipids are phospholipid-related materials, such as lecithin, phosphatidylethanolamine, lysolecithin,[etc] (col. 12, l/s. 8-29).

Belloni teach the term "therapeutically effective amount" refers to that amount of a biologically active substance which, when administered to a mammal in need thereof, is sufficient to effect treatment. The amount that constitutes a "therapeutically effective amount" **will vary depending on the substance, the condition or disease and its severity**, and the mammal to be treated, but may be determined routinely by one of ordinary skill in the art with regard to contemporary knowledge and to this disclosure (col. 6, l/s. 62-67).

Thus, it would have been prima facie obvious to one of skill in the art at the time of the invention to at once recognize a reasonable expectation of success via the incorporating together the teachings and inventive objectives of Eriksen et al, Koffas et al. (0110885) Makula, Koffas et al.(0137190 A1), Belloni et al.

Eriksen et al. essentially teach the limitations as cited in claim 18 and 21. General administration of a methanotroph-derived formulation with the apparent administration to a human subject is the central issue of the two instant claims. The language drawn to the lowering of LDL: HDL via the administration of microbial lipids is purely functional, principally. The administration of such compounds would produce any number of other modifications in the human or animal body in association with the disclosed language of reducing the LDL: HDL cholesterol ratio.

Makula provides motivation to combine based on its teaching drawn to a specific phospholipid which makes obvious the limitation of claim 37. Phosphatidylethanolamine is adequately indicated in Makula in view of the teachings of Eriksen.

Makula does not teach utility of phosphatidylethanolamine. The motivation to use phosphatidylethanolamine by Makula is resolved in Belloni examples which clearly teach examples of optional co-lipids are phospholipid-related materials, such as lecithin, phosphatidylethanolamine, lysolecithin, [etc] (col. 12, l/s. 8-29).

Belloni further provides the motivation to combine based on a therapeutically effective amount and the use for a mammal in need thereof.

Koffas et al. (USPGPUB 2002/0137190 A1) teach administration to fish of such food and feed formulations. Specifically, Koffas essentially teach that this capability will permit strains to be uniquely tailored for individual specific food and feed applications.

In light of the above, the one of skill would readily be inclined to recognize overlap and obviousness of invention based on the shared subject matter of all references cited.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Timothy E. Betton whose telephone number is (571) 272-9922. The examiner can normally be reached on Monday-Friday 8:30a - 5:00p. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Sreeni Padmanabhan can be reached on (571) 272-0629. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published

applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Shengjun Wang/
Primary Examiner, Art Unit 1617

TEB